REVIEW ARTICLE
https://doi.org/10.30773/pi.2025.0400
eISSN 1976-3026
OPEN ACCESS

Evolving Alzheimer's Disease Clinical Practice: Updated Diagnostic Criteria, Fluid Biomarkers, and Special Considerations for Anti-Amyloid Therapies

Hyun Woong Roh[1]*, Yoon Young Chang[2]*, Keun You Kim[3] ✉, So Yeon Jeon[4,5], Sheng-Min Wang[6], Eosu Kim[3], Jae-Nam Bae[7], and Seung-Ho Ryu[8]

[1]Department of Psychiatry, Ajou University School of Medicine, Suwon, Republic of Korea
[2]Department of Psychiatry, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea
[3]Department of Psychiatry, Institute of Behavioral Science in Medicine, Metabolism-Dementia Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Psychiatry, Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center, Seoul, Republic of Korea
[5]Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea
[6]Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[7]Department of Psychiatry, Inha University Hospital, Inha University College of Medicine, Incheon, Republic of Korea
[8]Department of Psychiatry, Konkuk University Medical Center, School of Medicine, Konkuk University, Seoul, Republic of Korea

Objective This review overviewed the recent paradigm shifts in the diagnosis and management of Alzheimer's disease (AD), emphasizing the 2024 Alzheimer's Association (AA) revised criteria, advances in cerebrospinal fluid (CSF) and blood-based biomarkers (BBMs), and practical considerations for anti-amyloid monoclonal antibody therapy.

Methods We conducted a narrative appraisal of consensus frameworks (2018 National Institute on Aging–Alzheimer's Association [NIA-AA] amyloid, tau, and neurodegeneration [AT(N)] and the 2024 AA criteria), clinical practice guidance from AA released in 2025, regulatory status of CSF and BBMs. Intended-use settings (triage vs. confirmatory) of BBMs and implementation of anti-amyloid antibody treatments (lecanemab or donanemab) in real-world practice in Korea were also reviewed.

Results The 2024 AA criteria define AD biologically and designate A and T as core biomarkers; Core 1 biomarkers can establish AD irrespective of symptoms, whereas Core 2 biomarkers refine staging. A two-cutoff BBM strategy (positive/intermediate/negative) reduces misclassification and guides confirmatory CSF/positron emission tomography (PET) or retesting. BBMs now approach CSF/PET accuracy for amyloid detection, enable triage and, in selected settings, confirmation, and show utility for monitoring treatment response. Integration of clinical stages (1–6) with biological stages (A–D) clarifies syndrome–pathology discordance. Special scenarios—maintenance after induction, APOE ε4 homozygotes, Down syndrome, and serious mental illness—require individualized risk–benefit assessment. In South Korea, constrained access to tau PET and some BBMs necessitates Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision–anchored evaluation with selective biomarker testing.

Conclusion Biomarker-oriented diagnosis and anti-amyloid therapies are reshaping AD care. Priorities include rigorous validation of BBMs across populations, equitable access to core biomarkers, safety strategies, and real-world evidence to implement maintenance and special-population care pathways.

Psychiatry Investig 2026;23(2):183-200

Keywords Dementia; Diagnosis; Geriatric psychiatry; Neurocognitive disorder; Neuroimaging.

INTRODUCTION

The evaluation and treatment of individuals with cognitive impairment in clinical practice is changing rapidly. The identification of amyloid, the core pathology of Alzheimer's disease (AD), has become easier after approval of ^{18}F-labelled

Received: November 6, 2025 **Accepted:** December 7, 2025

✉ **Correspondence:** Keun You Kim, MD, PhD
Department of Psychiatry, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
Tel: +82-2-2228-1620, **Fax:** +82-2-313-0891, **E-mail:** keunyou.kim@yonsei.ac.kr

*These authors contributed equally to this work.

tracers for positron emission tomography (PET).[1] Biomarkers in cerebrospinal fluid (CSF), such as total tau (t-tau), phosphorylated tau (p-tau), and amyloid-β42 (Aβ42), are elevated in patients with pathologically confirmed AD.[2] Blood-based biomarkers (BBMs), which were previously considered less accurate compared to CSF biomarkers,[2] have recently shown marked development.[3-5] Moreover, anti-amyloid antibody treatments, such as lecanemab and donanemab, have been approved in many countries since 2023, making the biological diagnosis of AD essential in the clinical practice rather than optional for research purposes.[6] While clinicians previously predicted the cause of cognitive impairment based on clinical symptoms and manifestations reported by patients or informants, it is now necessary to identify the underlying pathology to decide on the optimal treatment. Meanwhile, anti-amyloid antibodies as disease modifying treatment can induce significant adverse events.[7,8] Therefore, clinicians need to be more vigilant to patients' comorbidities and concomitant medications to minimize the unfavored results.

In this review, we summarized the major changes and clinical implications in the diagnostic criteria of AD, particularly in light of the recently revised criteria released in 2024.[9] We also reviewed the fluid biomarkers (CSF biomarker and BBM) for AD that are currently or will soon be available in real-world clinical practice. Furthermore, we explored various scenarios that may arise when applying anti-amyloid treatment.

MAJOR CHANGES IN DIAGNOSTIC CRITERIA FOR AD

Changes in diagnostic criteria for AD–emphasis on confirming pathology

The diagnostic criteria for AD have shifted from reliance on clinical symptom observation in the 20th century to a biologically defined framework grounded in neuroimaging and fluid biomarkers in the 21st century. Since Alzheimer[10] first identified amyloid plaques and neurofibrillary tangles in the postmortem brain tissue of a patient in 1906, the medical community has long regarded "AD" and "AD dementia" as essentially synonymous concepts.[11-17] This was largely because there had been no means of directly confirming pathology in living patients, and diagnosis was possible only after typical clinical symptoms appeared at the dementia stage. A turning point came with the advancement of PET and CSF analyses, which enabled visualization and quantification of amyloid and tau pathology in the living brain. These technologies revealed that AD-related pathological changes begin at least 10–20 years before the onset of clinical symptoms.[18] This discovery spurred efforts to distinguish AD from dementia due to AD,[19-22] and, with the subsequent demonstration of clinical efficacy for anti-amyloid antibody therapies, pathological confirmation has emerged as a central task not only in research but also in clinical practice. Consequently, the diagnostic paradigm of AD has been shifting its emphasis from clinical symptoms to pathological confirmation (Table 1).

Amyloid, tau, and neurodegeneration classification

The National Institute on Aging–Alzheimer's Association (NIA-AA) criteria, released in 2011, explicitly recognized that the pathological process of AD begins years before dementia symptoms appear.[12,15,23] Importantly, biomarkers were incorporated into the diagnostic algorithm to facilitate early and more accurate detection. These biomarkers included amyloid PET imaging, CSF Aβ42, CSF t-tau and p-tau, glucose metabolism on fluorodeoxyglucose PET, and characteristic patterns of cortical atrophy on structural MRI.[15,17] Nevertheless, significant barriers to the use of biomarkers in clinical practice include a lack of standardization, variability in interpretation, and limited availability, leading the NIA-AA criteria in 2011 to not recommend biomarkers for routine diagnostic purposes.

Building on these advances, the 2018 NIA-AA research framework redefined AD as a biological construct, distinct from clinical syndromes, by introducing the AT(N) classification system.[24] Within this model, individuals are categorized according to biomarker status for amyloid (A), tau (T), and neurodegeneration (N), with each component rated as positive or negative (A+/A-, T+/T-, N+/N-). A central tenet of this framework is that individuals who are both amyloid- and tau-positive (A+T+) are classified as having AD, irrespective of clinical presentation. In contrast, those with amyloid positivity but no tau pathology (A+T-) are considered to fall within the "Alzheimer's continuum," reflecting a biologically defined disease process that may or may not yet manifest clinically.[25] Prior to the 2018 framework, when an individual was suspected to have dementia owing to AD based on past history and clinical symptoms, 2011 NIA-AA criteria regarded him or her having "probable AD dementia" or "possible AD dementia."[15] However, under this framework, the diagnosis of AD is reserved only for cases where both amyloid and tau biomarkers are confirmed.[24] Cases exhibiting typical AD clinical symptoms but with unknown biomarker status are recommended to be labeled "Alzheimer's clinical syndrome." This framework is characterized by its emphasis on distinguishing between syndromes based on clinical symptoms and diseases based on biomarker status. However, this research framework was still intended to be used only in research, not in routine clinical practice.

Table 1. Past and present diagnostic criteria for AD

Year	Criteria announced by	Key features
1984	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[16]	First standardized diagnostic framework Based on clinical symptoms Categories: "Probable," "Possible," and "Definite" Neuropathological confirmation at autopsy
1980–2022	DSM[11,13,14]	Based on clinical symptoms DSM-III: "Alzheimer type dementia" DSM-5: Broader category of "major neurocognitive disorder"
2011	NIA-AA[12,15,17]	First integration of biomarkers : amyloid PET, CSF Aβ42, CSF tau, FDG PET, MRI Tripartite staging: AD dementia, MCI due to AD, preclinical AD
2018	NIA-AA[24]	Research framework Redefined AD as a biological construct, independent of clinical syndromes AT(N) classification: A (amyloid), T (tau), N (neurodegeneration)
2024	Alzheimer's Association (AA)[9]	Designed for clinical application Introduced Core 1 (early-change) and Core 2 (late-change) biomarkers Expanded AT(N) with I (immune/inflammatory), V (vascular injury), S (α-synucleinopathy) Dual staging: Biological (A–D) + Clinical (1–6) Formal incorporation of blood-based biomarkers
2024	International Working Group (IWG)[31]	Defines AD as a clinical–biological construct Diagnosis requires both cognitive impairment and biomarker evidence Asymptomatic biomarker-positive individuals classified as "at risk"

AD, Alzheimer's disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; NIA-AA, National Institute on Aging–Alzheimer's Association; PET, positron emission tomography; CSF, cerebrospinal fluid; Aβ, amyloid beta; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment.

Revised criteria for diagnosis and staging of AD by AA in 2024

Background for evolving revised criteria

With anti-amyloid antibody treatment gaining approval in multiple countries, starting with the United States and including South Korea, the need to standardize the diagnosis and staging of AD has grown significantly to ensure smooth communication in actual clinical practice. The accuracy of BBMs that detect AD-related pathologies, such as amyloid and tau, has improved remarkably. This also means that biologically diagnosing AD has become easier compared to existing methods like PET and CSF biomarkers. As existing brain imaging, CSF, and BBMs within the AT(N) category have become somewhat interchangeable, the need for updates has been raised.

Major changes in 2024 revised criteria

The 2018 criteria emphasized that they were a "research framework" intended solely for research purposes and not designed for clinical use.[24] However, the 2024 diagnostic criteria are intended for use in actual clinical practice.[9] The 2024 revised criteria defined A and T biomarkers as the "core biomarkers" for AD. These are subdivided further into Core 1 biomarkers, which change early in the disease course, and Core 2 biomarkers, which change relatively later. Notably, while 2018 criteria required both A and T biomarkers for diagnosing AD,[24] revised 2024 criteria can diagnose AD using Core 1 biomarkers (representing A) alone.[9] In revised 2024 criteria, BBMs were recognized as AD biomarkers, enabling improved cost-effectiveness and accessibility in the biological diagnosis of AD. Furthermore, as in the 2018 research framework, the 2024 revised criteria clearly distinguished between biological stages (A–D) and clinical stages (1–6) to enable integrated use (see sections "Biological staging of AD," "Clinical staging of AD," and "Integration of biological and clinical staging").

Biomarker categorization–A, T, N, inflammatory/immune mechanism, vascular brain injury, and alpha-synucleinopathy

The previous AT(N) biomarkers in 2018 have been expanded to include the categories of inflammatory/immune mechanisms (I), vascular brain injury (V), and alpha-synucleinopathy (S) (Table 2). T biomarkers have been further subdivided into T1 or T2 since the specific types increase at different stages

Table 2. Categorization of biomarkers in 2024 revised criteria

Biomarker category	CSF or plasma analytes	Imaging
Core biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T1 (phosphotylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T2 (AD tau proteinopathy)	MTBR-tau243, other p-tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation, astrocytic activation)	GFAP	
Biomarkers of non-AD copathology		
V (vascular brain injury)		Infarction on MRI or CT, WMH
S (α-synuclein)	αSyn-SAA	

p-tau231, p-tau205, MTBR-tau243, and non-p-tau fragments have not undergone the same level of validation testing as others. Reproduced from Jack et al. Alzheimers Dement 2024;20:5143-5169,[9] under the terms of the Creative Commons License (CC BY-NC-ND 4.0). CSF, cerebrospinal fluid; Aβ, amyloid beta; AD, Alzheimer's disease; p-tau, phosphorylated tau; MTBR, microtubule-binding region; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; αSyn-SAA, alpha-synuclein seed amplification assay; PET, positron emission tomography; FDG, fluorodeoxyglucose; WMH, white matter hyperintensity.

of AD. T1 biomarkers are those that change at a time point similar to that of early-stage amyloid PET in AD (p-tau217, 181, and 231). T2 biomarkers are tau that change at a time point similar to tau PET, i.e., at a relatively later stage (e.g., microtubule binding region [MTBR]-tau243).

Core biomarkers represent key indicators of neuropathological changes in AD, encompassing the A and T categories (Table 2). They are subdivided into Core 1 and Core 2 biomarkers based on the timing of abnormality and intended use.[9] Core 1 biomarkers are those that change at a time point similar to early-stage amyloid PET in AD (A, T1, hybrid combination). Core 2 biomarkers are those that change relatively later compared to Core 1 (tau PET and biofluid T2). The detection of abnormalities in Core 1 biomarkers allows for a diagnosis of AD, irrespective of clinical symptoms. However, not all Core 1 biomarkers are yet sufficiently accurate for routine clinical use.

Clinical implication of biomarker use

The results of AD biomarker tests should always be interpreted within the appropriate clinical context, as current biomarkers still have important limitations (e.g., lack of validated biofluid biomarkers, lower sensitivity and accuracy compared to neuropathological confirmation). Although biomarker testing could theoretically allow the diagnosis of AD in asymptomatic individuals, this revised criteria clearly emphasize that such testing should not be used for clinical purposes in asymptomatic patients at the present time.[9]

Coexisting pathologies beyond AD are common, so clinical judgment is always required to answer the question: "Can AD fully explain this patient's symptoms?" For instance, if a patient presents with Parkinsonian symptoms and hallucinations and tests positive for Core 1 biomarkers, the clinician must determine whether the cognitive decline arises from AD or from neuronal synuclein disease.[26] In such situations, Core 2 biomarker testing can provide valuable clarification. A positive Core 2 biomarker result indicates a substantial contribution of Alzheimer's pathology to the clinical picture, whereas a negative result suggests a limited role. Clinical judgment is equally essential when Core 1 biomarker findings do not align with the clinical presentation. For example, if the clinical features strongly suggest AD but the Core 1 biomarker is negative, further testing is required to resolve the inconsistency.

Biological staging of AD

According to the 2024 revised criteria, patients diagnosed with AD using Core 1 biomarkers can have their biological staging (A–D) determined based on amyloid and tau PET results (Table 3).[9] Biological staging based on fluid biomarkers is currently defined as "conceptual" and is only available for research purposes; it cannot be used in clinical practice. Revised 2024 criteria workgroup judged that biofluid biomarkers such as p-tau205, MTBR-tau243, and non-phosphorylated tau (np-tau) fragments as early, intermediate, and advanced-stage fluid markers required further validation for routine clinical use. In South Korea, neither tau PET nor fluid biomarkers are currently available for clinical use (only CSF

Table 3. Biological staging of AD in 2024 revised criteria

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
PET	Amyloid PET	Tau PET medial temporal region	Tau PET moderate neocortical uptake	Tau PET high neocortical uptake
	$A+T_{2-}$	$A+T_{2MTL+}$	$A+T_{2MOD+}$	$A+T_{2HIGH+}$
Core 1 fluid	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate* Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present.			

Staging may be accomplished by (1) a combination of amyloid PET and tau PET or (2) a combination of Core 1 fluid biomarkers (which would establish biological stage A or higher) plus tau PET (which would be used to discriminate between stages). The approach to determining A+ versus A- with amyloid PET may need special consideration in autosomal dominant AD and Down syndrome AD. Reproduced from Jack et al. Alzheimers Dement 2024;20:5143-5169,[9] under the terms of the Creative Commons License (CC BY-NC-ND 4.0). *accurate is defined as a minimum accuracy of 90% to detect abnormal amyloid PET in the intended-use population, or, more simply, plasma tests whose diagnostic performance is equivalent to that of approved CSF assays. AD, Alzheimer's disease; PET, positron emission tomography; CSF, cerebrospinal fluid; Aβ, amyloid beta; p-tau, phosphorylated tau.

fluid Core 1 biomarkers are available, see section "Regulatory approval status and future direction of CSF biomarkers"), making biological stage classification limited.

Clinical staging of AD

Clinical staging of AD is defined as stages 0 through 6 (Table 4).[9] This is largely consistent with what was first presented in the 2018 research framework.[24] While similar to the Global Deterioration Scale,[27] this clinical staging differs in that it was developed after the concept of disease-specific AD biomarkers was established. Compared to existing clinical stage terminology, subjective cognitive decline[28] corresponds to stage 2, mild cognitive impairment (MCI)[12] to stage 3, and mild, moderate, and severe dementia to stages 4, 5, and 6, respectively. Currently, lecanemab is approved for use in patients with MCI or mild dementia (with confirmed amyloid pathology),[29] corresponding to clinical stages 3 and 4.

Integration of biological and clinical staging

Patients diagnosed with AD using Core 1 biomarkers can be classified by combining their clinical stage (1–6) and biological stage (A–D). The clinical stage is listed first, followed by the biological stage (e.g., stage 2C). As shown in Table 5,[9] the two stages do not always correspond: advanced clinical symptoms (e.g., stage 6A) may coexist with an early biological stage. This reflects the principle of the revised 2024 criteria distinguishing biological pathology from clinical syndrome.[9] More severe clinical symptoms than biological stage suggest other pathologies additional to AD, whereas milder symptoms relative to biological stage may indicate greater cognitive reserve.[30]

International Working Group recommendation on revised AA criteria

According to the AA criteria, AD is diagnosed based solely on biomarker abnormalities.[9] In contrast, the International Working Group (IWG) conceptualized AD as a "clinical-biological construct" rather than a merely biological phenomenon.[31] The IWG articulated apprehensions regarding the AA's criteria that label cases as "AD" solely based on biomarker positivity regardless of symptoms, recommending the diagnosis only when biomarker positivity is confirmed alongside cognitive decline. While the AA also advised caution regarding biomarker testing in asymptomatic individuals, the IWG places even greater emphasis on this point. The diagnosis of AD in asymptomatic biomarker-positive individuals could be potentially problematic, as it is unclear when symptoms might emerge. Individuals who are cognitively normal yet exhibit biomarker positivity may live their entire lives without developing dementia. The diagnosis of such individuals offers no benefit when considering the social and psychological consequences.

Application of the revised criteria in clinical practice: recommendations from the Korean Association for Geriatric Psychiatry

The revised 2024 diagnostic criteria from the AA placed greater emphasis on the biological definition of AD than previous versions. This shift reflects the growing accessibility of biomarkers and the development of therapies targeting them. However, the IWG opposes this biomarker-only framework proposed by AA, recommending that the presence of clinical symptoms (cognitive impairment) remain essential for the diagnosis of AD. Moreover, in real-world clinical practice in South Korea, the use of Core 1 or Core 2 biomarkers remains limited. PET and CSF tests are costly or invasive, and among the Core 2 biomarkers, tau PET and amyloid/tau BBMs are currently available only for research purposes. Therefore, at present, the Korean Association for Geriatric Psychiatry (KAGP) currently recommends that patients with cognitive symptoms be evaluated for clinical severity of cognitive de-

cline using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria,[29,32] with biomarker testing considered only when AD is suspected as the underlying cause.

FLUID BIOMARKERS FOR AD

CSF biomarker

Comparison with PET biomarker

As well as a PET scan, the CSF test can accurately reflect

Table 4. Clinical staging of Alzheimer's disease in 2024 revised criteria

Stage	Features
Stage 0. Asymptomatic, deterministic gene*	No evidence of clinical change. Biomarkers in normal range.
Stage 1. Asymptomatic, biomarker evidence only	Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new symptoms.
Stage 2. Transitional decline: mild detectable change, but minimal impact on daily function	Normal performance within expected range on objective cognitive tests. Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months. May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range. May be documented through subjective report of cognitive decline. May be documented with recent-onset change in mood, anxiety, motivation not explained by life events. Remains fully independent with no or minimal functional impact on ADL
Stage 3. Cognitive impairment with early functional impact	Performance in the impaired/abnormal range on objective cognitive tests. Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments. Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).
Stage 4. Dementia with mild functional impairment	Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
Stage 5. Dementia with moderate functional impairment	Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
Stage 6. Dementia with severe functional impairment	Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

Reproduced from Jack et al. Alzheimers Dement 2024;20:5143-5169,[9] under the terms of the Creative Commons License (CC BY-NC-ND 4.0). *individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, decline in functional independence from baseline may be a more appropriate indicator of stage. ADL, activities of daily living.

Table 5. Integrated biological and clinical staging

	Stage 0	Clinical stage 1	Clinical stage 2	Clinical stage 3	Clinical stage 4–6
Initial biological stage (A)	X	1A	2A	3A	4–6A
Early biological stage (B)	X	1B	2B	3B	4–6B
Intermediate biological stage (C)	X	1C	2C	3C	4–6C
Advanced biological stage (D)	X	1D	2D	3D	4–6D

The typical expected progression trajectory is along the diagonal shaded cells, from 1A to 4–6D. However, considerable individual variability exists in the population. Individuals who lie above the diagonal (i.e., worse clinical stage than expected for biological stage) often have greater than average comorbid pathology. Individuals who lie below the diagonal (i.e., better clinical stage than expected for biological stage) may have exceptional cognitive reserve or resilience. Reproduced from Jack et al. Alzheimers Dement 2024;20:5143-5169,[9] under the terms of the Creative Commons License (CC BY-NC-ND 4.0).

Table 6. Comparison between CSF test and PET scan

	CSF	PET
Cost	Relatively low	High
Pathology confirmation range	Both amyloid and tau pathology can be assessed with a single test.	A single pathology per scan (amyloid or tau PET)
Invasiveness	Yes (requires lumbar puncture)	No
Exposure to radiation	No	Yes
Accessibility	The equipment is relatively simple. But a trained practitioner is needed for lumbar puncture.	Specialized personnel, including nuclear medicine specialists, and specialized equipment (PET scanners) are required.

CSF, cerebrospinal fluid; PET, positron emission tomography.

the pathology of the brain, including Aβ and tau. As the CSF test examines the body fluid surrounding the brain directly, it is known to reveal abnormal increases at an earlier stage of AD than PET scans.[33] The pros and cons of the CSF test compared to PET scans are presented in Table 6.

Major CSF biomarkers for diagnosis and staging of AD

Several CSF biomarkers are used for identifying AD-related pathology. CSF Aβ42/40 ratio is known to reflect the early cerebral amyloid deposit. Aβ42, the isoform of Aβ comprising 42 amino acids, is prone to aggregate more readily than Aβ40 and to form Aβ oligomers, fibrils, and neuritic plaques.[34] Aβ40 is the most abundant isoform and is more soluble than Aβ42.[35] In AD, pathologic Aβ42 remains aggregated in the brain parenchyma and not secreted to CSF, probably through glymphatic system, resulting in the reduced level of Aβ42 in CSF.[36] Thus, a decreased CSF Aβ42/40 ratio demonstrates a high degree of concordance (over 90%) with amyloid PET positivity.[34,36,37]

CSF t-tau is the first biomarker reported for tau pathology in AD.[38] Although the level of CSF t-tau is higher in AD patients than in healthy controls, it is also increased in other neurodegenerative diseases (e.g., frontotemporal dementia, dementia with Lewy bodies, and vascular dementia)[39] and in acute brain injuries that are not clearly related to tauopathy (e.g. Creutzfeldt-Jakob disease,[40] traumatic brain injury,[41] and ischemic stroke[42]). Due to this lack of clarity surrounding t-tau, which can increase in both AD-related neurodegeneration and non-specific brain damage, the revised criteria from the AA did not include t-tau in either T or N categories.[9]

CSF p-tau is thought to indicate the pathologic form of tau,[39] as hyperphosphorylation results in the aggregation of tau and the formation of neurofibrillary tangles.[43] Following the initial CSF p-tau study was presented in 1995 by Blennow et al.,[44] CSF p-tau181, tau phosphorylated at threonine 181, has been studied extensively for biomarker of AD.[45,46] However, recent studies reported that p-tau217 is more accurate than p-tau181 for AD diagnosis such as amyloid and tau PET positivity.[47,48] Other observational studies identified that CSF p-tau231 levels increased in the very early stage of AD at a similar time to, or faster than, p-tau217.[49,50] Although they are tau biomarkers, p-tau181, p-tau217, and p-tau231 are observed to rise during the early stages of AD, when Aβ begins to deposit and amyloid PET scans become positive. Meanwhile, CSF p-tau205 is known to increase in later stage of AD, together with t-tau, when neuronal dysfunction occurs.[51,52]

MTBR-tau243 is a recently identified CSF biomarker that shows an abnormal increase in a late stage of AD and tauopathy.[53-55] According to Horie et al.,[54] CSF p-tau181, p-tau217, and p-tau231 levels were associated with amyloid PET rather than tau PET, while CSF MTBR-tau243 levels were associated with tau PET rather than amyloid PET. Similarly, CSF MTBR-tau243 was linearly associated with tau PET, while CSF p-tau217 exhibited a steep increase during the early Braak stage of tau PET, eventually forming a relative plateau.[54]

CSF np-tau, different from t-tau that includes both np-tau and p-tau, serves as a biomarker that represents tau tangle formation and neurodegeneration in a later stage of AD.[56]

Sequence of CSF biomarker abnormality by AD progression

Based on the incorporation of observational studies, CSF biomarkers seem to become abnormal in the following sequence as AD progresses: CSF Aβ42/40 ratio, p-tau217 (or p-tau181 or p-tau231), p-tau205, MTBR-tau243, and np-tau.[49,50,56] The former biomarkers represent amyloid pathology, and the latter represent tau pathology.

Regulatory approval status and future direction of CSF biomarkers

Three hybrid combination biomarkers, including CSF Aβ42/40 ratio, t-tau/Aβ42 ratio, and p-tau181/Aβ42 ratio, have received regulatory approval from the United States Food and Drug Administration (FDA) and European Medicines Agency.[50] These are also Core 1 biomarkers in the re-

vised criteria by AA (Table 2). Of those, the Korean Ministry of Food and Drug Safety approved Roche's Elecsys Aβ42 and p-tau181 in 2023, and t-tau in 2024.[57,58] As anti-amyloid antibody therapies are introduced, confirming AD pathology is now clinically essential. CSF testing is therefore expected to become more common among patients who are burdened by PET scans and uncomfortable with radiation exposure. The regulatory approval status of CSF and PET biomarkers in Korea, the United States, Europe, and Japan is presented in Table 7.

BBM

Comparison with PET and CSF biomarker

PET and CSF biomarkers demonstrate high accuracy in detecting brain amyloid or tau pathology. However, PET imaging is costly and requires specialized equipment (PET scanner) for each clinic. CSF biomarker testing requires a lumbar puncture, which is invasive. BBMs, on the other hand, do not need specialized equipment and are less invasive, making them more accessible than PET or CSF biomarkers. Although attempts to detect AD pathology in plasma or serum via conventional technique (such as ELISA or xMAP) showed mixed results,[2] recent studies presented high accuracy comparable to PET or CSF.[3,59,60] This development is owing to the introduction of new assay techniques, such as immunoprecipitation mass spectrometry (IP/MS), single molecule array (Simoa), electrochemiluminescence immunoassay, and chemiluminescent enzyme immunoassay.[37,61,62]

Major BBMs for diagnosis and staging of AD

Plasma Aβ42/40 ratio can identify the early cerebral amyloid deposition, as can the CSF Aβ42/40 ratio. It is known to convert abnormal earlier than amyloid PET in the course of AD progression.[63] However, when comparing amyloid PET (+) and (-) cases, CSF Aβ42/40 ratio decreased by approximately 50%, whereas plasma Aβ42/40 decreased by only about 10%–15%.[64] This smaller fold change in plasma Aβ42/40 ratio leads to the relatively lower diagnostic accuracy for confirming the presence or absence of cerebral amyloid pathology.

Plasma p-tau217 is a tau isoform that is elevated in the presence of early amyloid deposition and can even reflect the presence of later tau pathology.[9,60,65,66] To date, it is the most accurate BBM for detecting amyloid PET positivity.[66,67] Unlike plasma Aβ42/40 ratio, for which there is only a 10%–15% difference between amyloid PET (+) and (-) individuals, p-tau217 shows a difference of 300%–700%, making it a more suitable diagnostic tool for AD.[64,68] Like amyloid PET, plasma p-tau217 is a strong predictor of progression to MCI in cognitively unimpaired individuals.[69] Recent studies indicate that the ratio of plasma p-tau217 to np-tau217 (%p-tau217) is more accurate than p-tau217 alone, and that the accuracy of %p-tau217 is not affected by age, unlike p-tau217.[70] Plasma %p-tau217 can be equal or even superior to FDA-approved CSF biomarkers for detection of amyloid PET positivity.[60] Other studies suggest that plasma p-tau217/Aβ42 ratio may be more accurate than p-tau217 alone in detecting amyloid pathology.[71-73] In light of this high accuracy, plasma p-tau217 is considered as a Core 1 biomarker in the revised criteria of AD from AA.[9] In addition, plasma p-tau217 has potential to reflect later tau pathology and cognitive impairment.[74,75] This indicates that plasma p-tau217 could be used as a staging biomarker of AD.

Plasma p-tau181 is a biomarker that has been studied earlier than other biomarkers, as well as CSF p-tau181. It has dem-

Table 7. Regulatory approval status of CSF or PET biomarkers for Alzheimer's disease diagnosis

Biomarker	Brand name (manufacturer)	Type	Regulatory approval status			
			Korea MFDS	U.S. FDA	EMA	Japan PMDA
Florbetapir	Amyvid (Eli Lilly)	Amyloid PET	X	O	O	O
Flutemetamol	Vizamil (GE HealthCare)	Amyloid PET	O	O	O	O
Florbetaben	Neuraceq (Life Molecular Imaging)	Amyloid PET	O	O	O	O
Florapronol	Alzavue (Futurechem)	Amyloid PET	O	X	X	X
Flortaucipir	Tauvid (Eli Lilly)	Tau PET	X	O	O	O
p-tau181/Aβ42	Elecsys (Roche)	CSF	O	O	O	O
t-tau/Aβ42	Elecsys (Roche)	CSF	O	O	O	X
Aβ42/40	Lumipulse (Fujirebio)	CSF	X	O	O	O
p-tau181	Lumipulse (Fujirebio)	CSF	X	X	O	O
t-tau	Lumipulse (Fujirebio)	CSF	X	X	O	O

CSF, cerebrospinal fluid; PET, positron emission tomography; MFDS, Ministry of Food and Drug Safety; FDA, Food and Drug Administration; EMA, European Medicines Agency; PMDA, Pharmaceuticals and Medical Devices Agency; p-tau, phosphorylated tau; Aβ, amyloid beta; t-tau, total tau.

onstrated high accuracy in detecting amyloid and tau pathology.[76] However, compared with plasma p-tau217, plasma p-tau181's accuracy to detect amyloid PET positivity is lower.[67] Plasma p-tau231 is known to be elevated in the early stage of amyloid deposition.[65,77] After increasing in the early stage, it remains at a plateau in the later stage of AD.[78]

Plasma p-tau205 and endogenous MTBR-tau243 (eMTBR-tau243) reflect tau pathology in the later stage of AD.[65,79] Especially, a recent study demonstrated that plasma eMTBR-tau243 showed strong association with tau PET uptake rather than amyloid PET uptake, outperforming other plasma tau biomarkers including p-tau217.[80] Plasma p-tau205 and eMTBR-tau243 are Core 2 biomarkers which can be used to represent AD-related tauopathy.[9]

Neurofilament light chain (NfL) is a subunit of axonal neurofilament which is released into CSF or blood during neurodegeneration or axonal injury. As a "N (neurodegeneration)" biomarker in the revised criteria for AD,[9] increased plasma NfL can predict future cognitive decline or hippocampal atrophy.[81] Plasma NfL increases not only in AD but also in other CNS-related diseases such as frontotemporal dementia, vascular dementia, HIV-associated dementia, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, and parkinsonian disorders.[82,83]

Glial fibrillary acidic protein (GFAP) is a component of the cytoskeleton in astrocytes. Plasma GFAP is an indicator of the degree of neuroinflammation since the number and size of astrocytes increase due to inflammatory or immune responses. GFAP is an "I (inflammation)" marker in the revised criteria for AD.[9] It does not increase specifically in Alzheimer's pathology and, like NfL, also increases in other degenerative brain diseases such as frontotemporal dementia or Lewy body dementia.[82]

Two cut-off approach using BBMs

When using a single cut-off value to determine amyloid positivity via BBM, some patients will have BBM levels close to the threshold. Since measurements may vary slightly between repeat tests for the same patient, if a measurement is near the cut-off threshold, the result could change if repeat testing is performed. To minimize the risk of false positive or false negative results, Global CEO Initiative on Alzheimer's Disease BBM workgroup recommended using two cut-off approach to classify BBM tests into three categories: positive, intermediate, and negative (Figure 1).[3,4,84] Patients with a "positive" BBM result are interpreted as having amyloid pathology, while those with a "negative" result are interpreted as having no amyloid pathology. Patients with an "intermediate" BBM result may consider confirmatory amyloid PET or CSF testing, or repeat BBM testing after 1 year.[4] When using two cut-off approach, the BBM workgroup recommended that the BBM should be accurate enough to minimize the number of individuals with an "intermediate" result to no more than 15%–20% of the entire test population.

Application of BBMs in real-world clinical settings

BBMs can be used as a triage test to determine the presence or absence of amyloid pathology and to screen candidates for

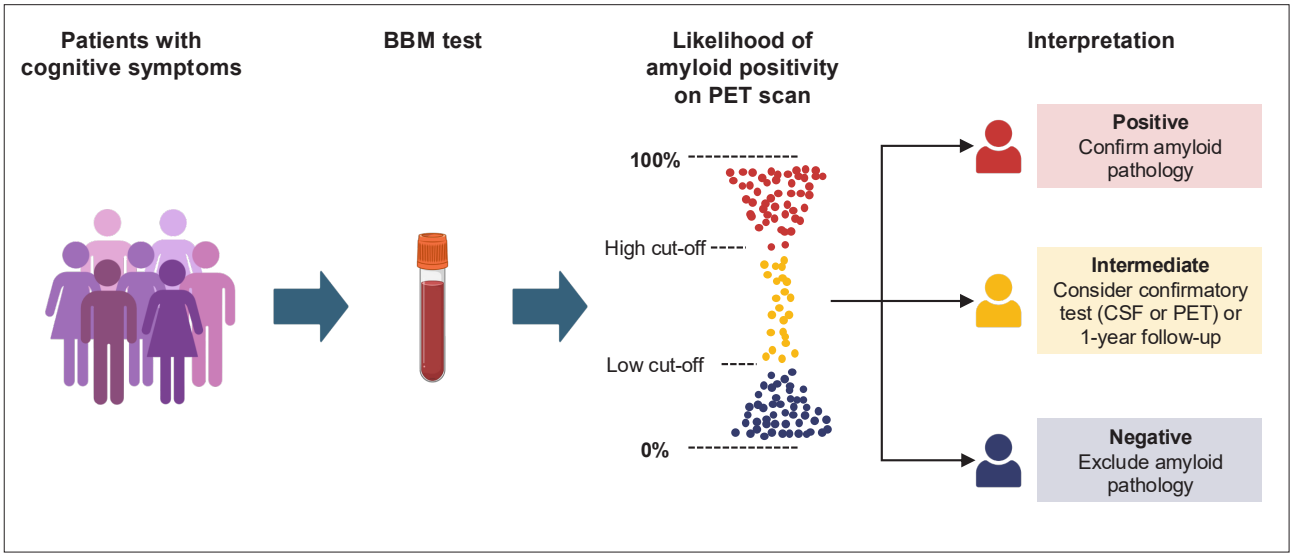

Figure 1. The two cut-off approach to using blood-based biomarker (BBM) to identify amyloid pathology. The two-cut-off approach categorises BBM test results into three groups. A positive result (high probability) confirms amyloid pathology, while a negative result (low probability) rules it out. In intermediate cases, consider an amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) scan as a confirmatory test. If not urgent, consider retesting the BBM in 1 year. Intermediate cases should account for no more than 15%–20% of cases and be accurate enough to be utilised as a BBM. Reproduced from Brum et al. Nat Aging 2023;3:1079-1090,[84] under the terms of the Creative Commons License (CC BY-NC-ND 4.0).

anti-amyloid antibody treatment.[3,5] As a triage test, the BBM test can produce two results: a negative result rules out AD pathology with high probability, while a positive result must be confirmed by amyloid PET or CSF tests.[5] Patients with cognitive symptoms can undergo a clinical evaluation, including a physical examination, history taking, and neuropsychological testing. If AD is suspected as a result of the initial assessment, BBM testing alongside a brain MRI or CT scan can be further assessed. BBM test results require CSF or PET tests to confirm amyloid pathology. If amyloid pathology is confirmed, anti-amyloid antibody treatment may be considered.[3] The BBM Workgroup organized by the Global CEO Initiative on AD recommended that, in secondary care, BBM tests need to be conducted under the following conditions: objective cognitive impairment, suspected AD pathology after comprehensive assessment, and expected improvement in management of cognitive impairment.[4] In primary care, since younger patients in primary care usually have a low chance of amyloid pathology, this BBM Workgroup recommended using BBM as a triage test in primary care only for those who are 55 years old or older.[4] The Alzheimer's Association Clinical Practice Guideline similarly recommended the use of BBM only when knowing whether AD pathology is useful for shared decision making with the patient in secondary care or specialized memory clinic where memory disorder specialists are involved.[5]

BBMs can be used as a confirmatory test in which a negative result excludes amyloid pathology, and a positive result confirms AD pathology without the need for further confirmatory tests. After physical examination, history taking, and neuropsychological testing in patients with cognitive symptoms, a confirmatory BBM test is available if AD is suspected. When amyloid pathology is confirmed by BBM, anti-amyloid antibody treatment can be considered.[3] The recommendation from the BBM Workgroup organized by the Global CEO Initiative on a confirmatory BBM test in a secondary care is same as a triage test.[4] In primary care, this BBM Workgroup recommended use of BBM for confirming amyloid pathology for those aged 65 or older.[4] The Alzheimer's Association Clinical Practice Guideline did not distinguish between confirmatory and triage tests in terms of clinical use recommendations. Regardless of its purpose (triage or confirmation), BBM may be inappropriate if knowing whether AD pathology is present would be of little utility.[5] This utility of the test could be either patient preference, diagnostic or prognostic value, or the treatment decision-making. The Alzheimer's Association Clinical Practice Guideline only focused on secondary care settings, due to need for gathering further evidence in primary care.[5]

BBMs can also be used to monitor treatment response of anti-amyloid antibody treatment. Lecanemab elevated plasma Aβ42/40 ratio and reduced p-tau181 and GFAP in phase 3 clinical trials.[7] Donanemab reduced plasma p-tau217.[8] After successfully reducing amyloid with antibody therapy, periodic BBM scans can be used to determine if amyloid pathology is re-accumulating, and then discuss whether to restart antibody therapy.

Required accuracy of BBM for detecting amyloid pathology

According to the revised diagnostic criteria by the AA in 2024, an "accurate" BBM eligible for inclusion in Core 1 biomarkers must have an amyloid PET positive detection accuracy of 90% or higher in intended-use population, which is equivalent to CSF biomarkers.[9] Accuracy is defined as (true positive+true negative)/(true positive+true negative+false positive+false negative) at a given threshold or cut-off.

In July 2024, the BBM Workgroup by the Global CEO Initiative on AD recommended that the minimum performance of a triage BBM test should be a sensitivity of 90% and a specificity of 85% in primary care, and 75%–85% in secondary care. As a confirmatory test, the BBM test should have sensitivity and specificity of at least 90%.[4]

In the Alzheimer's Association Clinical Practice Guideline revealed in July 2025, the performance of BBM detecting amyloid pathology should be at least 90% sensitivity and a 75% specificity to be used as a triage test.[5] This is intended for limited use in specialized memory clinics, where the prevalence of amyloid-positive patients is expected to be higher than in primary care settings. To perform as a confirmatory test, the BBM test requires a minimum sensitivity and specificity of both 90%.[5] The BBM tests that currently meet the criteria are listed in Table 8.

Regulatory approval status of BBMs

In May 2025, FDA cleared the Lumipulse G p-tau217/Aβ42 Plasma Ratio with two cut-off approach as the first in vitro diagnostic device to aid the diagnosis of AD.[85] Additionally, various BBMs are under FDA's Breakthrough Device Program, which can accelerate the approval process (Table 9).[86] Currently, BBM is being used in clinical trials for monitoring the response of anti-amyloid antibody treatments such as lecanemab, donanemab, and trontinemab.[7,8,87] Beyond those listed in Table 9, BBMs meeting criteria suggested by the Alzheimer's Association Clinical Practice Guideline or the Global CEO Initiative could be used in future clinical trials. The revised diagnostic criteria in 2024 stated that amyloid PET detection with an accuracy of 90% or higher can be used for AD diagnosis and biological stage assignment.[9]

SPECIAL CONSIDERATIONS

Our previous guideline publication addressed the fundamental principles of patient selection for anti-amyloid antibody therapy, including inclusion and exclusion criteria and major comorbidities relevant to amyloid-related imaging abnormalities (ARIA) monitoring.[29] Those recommendations remain essential for routine practice. In the present review, we extend this framework by exploring issues that were only briefly mentioned or not sufficiently elaborated previously, such as long-term maintenance strategies, genotype-specific dosing, and the nuanced challenges faced by individuals with Down syndrome or serious mental illness. Drawing upon the Practical Guide of the KAGP to Anti-Amyloid Monoclonal Antibody Therapy for Alzheimer's Disease (2025) and newly available clinical evidence, we aim to provide a more detailed discussion of these special considerations and to highlight additional dilemmas likely to emerge in real-world settings.

Long-term maintenance therapy after 18 months

In phase 2 study 201 and its open-label extension, 18 months of lecanemab treatment led to robust reductions in amyloid PET burden. When treatment was discontinued, however, amyloid re-accumulated, with approximately 21% of the reduction lost by 24 months.[88] These findings indicate that while lecanemab is highly effective at reducing amyloid, continuous dosing is likely required to sustain low amyloid levels.

Pharmacokinetic and pharmacodynamic modeling based on the extension data further suggested that monthly intravenous dosing could maintain these reductions after the induction phase. On January 2025, the U.S. FDA approved a maintenance regimen of intravenous infusion once every 4 weeks for patients completing the 18-month biweekly course.[89] Thus, both every 2 weeks and every 4 weeks of intravenous dosing are now considered viable options for maintenance therapy, with local regulatory review expected in South Korea. Moreover, the U.S. FDA approved weekly subcutaneous dosing for maintenance treatment in August 2025.[90] Regarding that a weekly subcutaneous dosing as an initial treatment is in the course of approval review after being granted fast track status,[91] more convenient methods will be available in the near future.

For comparison, donanemab followed a different maintenance strategy. In the TRAILBLAZER-ALZ 2 trial, donanemab was administered every 4 weeks, and patients underwent amyloid PET every 6 months. When plaques were reduced to minimal levels, treatment was switched to placebo, reflecting that its therapeutic target is amyloid plaque itself.[8] The FDA similarly advises that donanemab may be discontinued in practice once amyloid PET confirms clearance, with biomarkers such as blood-based measures used to monitor for re-accumulation. Together, these findings illustrate two distinct approaches: lecanemab considering continuous maintenance to prevent rebound, and donanemab adopting a biomarker-driven discontinuation paradigm.

APOE ε4 homozygotes and dosing strategies

APOE ε4 homozygotes are known to have a markedly elevated risk of ARIA compared with noncarriers, a fact consistently demonstrated across anti-amyloid antibody trials.[92] Accordingly, although various dosing strategies have been considered to mitigate this risk, no definitive guideline has yet been established.

The TRAILBLAZER-ALZ 6 randomized trial tested a modified titration schedule of donanemab against the standard regimen. Patients in the titration group experienced significantly fewer ARIA-E events (15.6% vs. 24.2%), and radiographic severity was lower, while amyloid reduction and overall safety outcomes remained comparable between the groups.[93] Although the published report did not provide detailed subgroup analyses for APOE ε4 homozygotes, earlier observations suggest that this population may derive particular benefit from titration. Nevertheless, in the absence of de-

Table 8. Blood-based biomarker tests that met requirements for the Alzheimer's Association Clinical Practice Guideline in specialized memory clinic (secondary care)

Triaging test	Confirmatory test
%p-tau217 IP-MS WashU	%p-tau217 IP-MS WashU
%p-tau217 IP-MS Precivity™, C2N Diagnostics	p-tau217 Immunoassay Lumipulse, Fujirebio
p-tau217 IP-MS Precivity™, C2N Diagnostics	
p-tau217 Immunoassay Lumipulse, Fujirebio	
Aβ42/40 Immunoassay HISCL, Sysmex	

The data was accessed on September 9, 2025. The results may change based on the systematic review which will be updated at https://app.magicapp.org/#/guideline/nyO1Yj. This review is being conducted by the Alzheimer's Association Clinical Practice Guideline.[5] %p-tau217, phosphorylated tau 217 to non-phosphorylated tau 217 ratio; IP-MS, immunoprecipitation mass spectrometry; WashU, Washington University; Aβ, amyloid beta.

Table 9. Regulatory status of blood-based biomarkers for Alzheimer's disease diagnosis

Test name	Analytes	Manufacturer	Assay	Regulatory status			
				Korean MFDS	U.S. FDA	Europe (EU CE or UK MHRA)	Japan PMDA
Lumipulse G p-tau217/β-Amyloid 1-42 Plasma Ratio	p-tau217/Aβ42 ratio	Fujirebio Diagnostics	CLEIA		IVD approval[85]		
PrecivityAD2™	Aβ42/40 ratio, %p-tau217 (algorithm-based APS2 score)	C2N Diagnostics	IP-MS			MHRA Medical Device Certification[a]	
PrecivityAD®	Aβ42/40 ratio, APOE profile, age (algorithm-based APS score)	C2N Diagnostics	IP-MS		Breakthrough Device Designation[b]	CE Mark[c]	
Elecsys® p-tau181	p-tau181	Roche Diagnostics	ECLIA			CE Mark[d]	
Elecsys® p-tau217	p-tau217	Roche Diagnostics	ECLIA		Breakthrough Device Designation[e]		
Elecsys® Amyloid Plasma Panel	p-tau181 and APOE profile	Roche Diagnostics	ECLIA		Breakthrough Device Designation[f]		
Simoa® p-tau181 blood test	p-tau181	Quanterix Corporation	Simoa		Breakthrough Device Designation[g]		
DxI 9000™ Access Immunoassay Analyzer	ptau217/Aβ42	Beckman Coulter Diagnostics	Chemiluminescent Immunoassay		Breakthrough Device Designation[h]		
Spear Bio's p-tau217 blood test	p-tau217	SpearBio	SPEAR technology		Breakthrough Device Designation[i]		
Simoa® p-tau217 blood test	p-tau217	Quanterix Corporation	Simoa		Breakthrough Device Designation[j]		
HISCL™ Aβ42/40 Assay Kit	Aβ42/40 ratio	Sysmex Corporation	CLEIA			CE Mark[k]	IVD approval[l]
AlzOn (inBlood oligomerized Aβ Test)	Oligomerized Aβ	PeopleBio	Multimer Detection System	IVD approval			
QPLEXTM Alz plus assay	Aβ40, galectin3 binding protein, angiotensin-converting enzyme, periostin	QuantaMatrix		IVD approval			

Breakthrough Device Program is a voluntary pathway that speeds up development, assessment, and review of medical devices that offer more effective treatment or diagnosis for life-threatening or irreversibly debilitating diseases.[86] [a]https://c2n.com/news-releases/c2n-diagnostics-precivityad2-blood-test-receives-mhra-medical-device-certification-in-the-united-kingdomnbsp; [b]https://precivityad.com/news/c2n-diagnostics-reports-high-accuracy; [c]https://c2n.com/media-coverage/2020/12/09/2020-12-8-precivityad-blood-tests-reach-expands-to-europe-and-california-following-initial-launch-test-detects-alzheimers-disease-pathology; [d]https://www.roche.com/media/releases/med-cor-2025-07-23b; [e]https://www.roche.com/media/releases/med-cor-2024-04-11; [f]https://www.roche.com/media/releases/med-cor-2022-07-19; [g]https://www.quanterix.com/press-releases/quanterix-granted-breakthrough-device-designation-from-u-s-fda-for-blood-based-ptau-181-assay-for-alzheimers-disease/; [h]https://www.beckmancoulter.com/about-beckman-coulter/newsroom/press-releases/2025/q1/2025-jan28-bec-receives-fda-breakthrough-device-designation; [i]https://spear.bio/blog/2025/01/13/spear-bio-secures-fda-breakthrough-device-designation-for-its-novel-ptau-217-blood-test-advancing-scalable-solutions-for-early-alzheimers-disease-diagnosis/; [j]https://www.quanterix.com/press-releases/quanterix-granted-breakthrough-device-designation-from-u-s-fda-for-blood-based-p-tau-217-test-for-alzheimers-disease/; [k]https://www.sysmex.co.jp/en/news/2023/231225.html; [l]https://www.sysmex.co.jp/en/news/2022/221222.html. MFDS, Ministry of Food and Drug Safety; FDA, Food and Drug Administration; CE, Conformité Européenne; MHRA, Medicines and Healthcare products Regulatory Agency; PMDA, Pharmaceuticals and Medical Devices Agency; p-tau, phosphorylated tau; Aβ, amyloid beta; APS, amyloid probability score; CLEIA, chemiluminescent enzyme immunoassay; IP-MS, immunoprecipitation mass spectrometry; ECLIA, electrochemiluminescence immunoassay; Simoa, single molecule array; SPEAR, Successive Proximity Extension Amplification Reaction; IVD, in vitro diagnostic.

finitive trial data, it remains uncertain whether modified dosing strategies reliably mitigate the excess risk in ε4 homozygotes.

For lecanemab, recent appropriate use recommendations and updated safety analyses have underscored the increased risk of ARIA in APOE ε4 homozygotes, but no titration-based dosing strategies have been proposed to date.[92,94] Ongoing prevention trials such as AHEAD 3-45 are exploring alternative dosing regimens, including lower or less frequent administration in cognitively unimpaired individuals, but these studies are not specifically designed to establish genotype-based titration strategies.[95] Due to the emergence of ARIA in the early treatment phase, the U.S. FDA recently (in August 2025) recommended an additional MRI monitoring before 3rd IV infusion, whereas the pre-existing recommendation was for MRI scans before 5th, 7th, and 14th infusions.[96] Future studies will find the risk factors of ARIA and the impact of dose adjustment in this high-risk group.

Down syndrome: at risk of being overlooked in treatment planning

The vast majority of individuals with Down syndrome develop amyloid pathology by mid-adulthood, and AD typically manifests at an earlier age compared with sporadic cases.[97] Comorbidities such as vascular risk factors, epilepsy, and autoimmune conditions are also more prevalent, complicating both diagnosis and therapeutic decision-making.[98,99]

Despite this elevated risk, people with Down syndrome have been almost universally excluded from clinical trials of disease-modifying therapies for AD. As a result, there is little direct evidence on the safety or efficacy of monoclonal antibodies in this population. Concerns about heightened vulnerability to adverse effects, including ARIA or infusion-related reaction, must therefore be balanced against the ethical imperative to provide access to potentially disease-modifying treatment.

Systemic barriers and diagnostic overshadowing can further limit access to care. Intellectual disability and psychiatric comorbidities may delay recognition of dementia symptoms, leading to missed opportunities for timely diagnosis and intervention. These challenges underscore the need for tailored screening and treatment guidelines and dedicated research efforts. In the meantime, clinicians should adopt a cautious, individualized approach, emphasizing shared decision-making with families and caregivers.

Serious mental illness: challenges in treatment access and decision-making

Patients with serious mental illness, such as schizophrenia and bipolar disorder, pose unique challenges when considering anti-amyloid antibody treatment. While many individuals remain clinically stable for extended periods, episodes of symptom exacerbation can impair judgment and decision-making capacity, complicating both the recognition of cognitive decline and adherence to treatment protocols. In routine clinical settings, these issues may not be readily apparent, as psychiatry lacks objective laboratory markers for disease activity. Close collaboration with psychiatrists is therefore essential to ensure accurate assessment of mental status, evaluate treatment readiness, and anticipate fluctuations in capacity over time.

People with severe psychiatric disorders have also been disproportionately excluded from AD clinical trials, leading to a paucity of evidence on the safety and efficacy of monoclonal antibodies in this population. This exclusion may inadvertently reinforce disparities, particularly given the elevated burden of vascular and metabolic comorbidities that already increase dementia risk in these patients.[100] From an ethical perspective, clinicians face a dual challenge. On one hand, there are legitimate concerns regarding patients' ability to provide ongoing informed consent, maintain adherence, and tolerate adverse events such as ARIA or infusion-related reactions. On the other hand, excluding patients solely because of a psychiatric diagnosis risks deepening existing inequities in care, particularly when individuals retain clear decision-making capacity. In such cases, opportunities for disease-modifying therapy should not be denied automatically but instead considered through individualized assessment and shared decision-making, with active involvement of caregivers and psychiatrists.

Other uncertainties: clinical dilemmas likely to arise in clinical practice

Despite accumulating trial data, several important clinical dilemmas remain insufficiently addressed by current guidelines. These scenarios were rarely represented in clinical studies, where exclusion criteria limited the inclusion of medically complex patients, but they are almost certain to emerge in real-world practice.

One such situation involves the new diagnosis of malignancy during anti-amyloid antibody therapy. In the absence of trial evidence, oncologic treatment is generally prioritized, with antibody therapy suspended while systemic disease is addressed. While this pragmatic approach avoids competing toxicities, there is no clear evidence on whether and when therapy can be safely restarted. In addition, many cancer therapies can alter hematopoietic function or increase bleeding risk, which may further compound the potential for ARIA-H. The growing use of immuno-oncologic agents also raises the possibility of unforeseen pharmacologic or immunologic

interactions, an area where virtually no data currently exist.

Acute vascular events raise even more urgent challenges. In myocardial infarction or ischemic stroke, reperfusion therapies such as percutaneous coronary intervention, anticoagulation, thrombolysis, or endovascular procedures must be initiated without delay, given the critical importance of time to treatment. One published case has documented fatal intracerebral hemorrhage in a patient on lecanemab who received thrombolytic agent for stroke, illustrating the risk.[101] Yet emergent reperfusion therapy cannot be withheld in golden-time emergencies, leaving clinicians in unavoidable dilemmas. Similar concerns extend to atrial fibrillation newly diagnosed during lecanemab therapy, where the need for anticoagulation conflicts with current recommendations to avoid therapeutic anticoagulation in patients receiving anti-amyloid antibodies. A recent case report described management of such a situation through left atrial appendage closure as an alternative to long-term anticoagulation.[102] These examples illustrate how real-world practice will repeatedly confront high-stakes decisions in the absence of trial data. Ongoing accumulation of clinical experience and registry-based evidence will be essential to inform future guidance.

DISCUSSION

In the emergence of disease-modifying treatments, this review focused on the major changes in the field of AD: diagnostic criteria, biomarkers for AD pathology, and potential scenarios for anti-amyloid monoclonal antibody treatments. Interpretation of biomarker results in combination with clinical presentation became much more important regarding the various treatment options. Clinicians who care for patients with cognitive symptoms need to know the recent paradigm shift of AD diagnosis and treatment.

According to the revised 2024 criteria by AA, AD is not a clinical syndrome anymore, but a biologically defined disease.[9] According to these criteria, asymptomatic individuals with biomarker positive are diagnosed to have AD. However, the psychological and ethical burden and the cost-benefit ratio of the diagnosis imposed on them remain uncertain. Therefore, there are concerns, notably raised by IWG, that referring to the preclinical stage as a "diagnosis" is problematic.[31,103] Actually, the effect of anti-amyloid antibody treatment, such as lecanemab and donanemab, on asymptomatic individuals is being investigated in clinical trials.[6,95,104] Routine clinical use of biomarker for AD diagnosis is not recommended until the results of these trials have been fully analyzed and the performance of the biomarkers is guaranteed.

CSF biomarkers are the gold standard surrogate for the diagnosis of AD. In real-world clinical practice in South Korea, CSF biomarkers remain the only way to evaluate the stage of AD via tau pathology, as tau PET is not yet available for routine clinical use (Table 7). Nevertheless, lumbar puncture is a relatively invasive, time-consuming, and requires a skillful physician supported by a well-trained assistant. Alternatively, BBMs are accumulating growing evidence to serve as a standalone marker for the diagnosis of AD. With the recent approval of the Lumipulse G p-tau217/Aβ42 plasma ratio by U.S. FDA (the first BBM to receive such authorization), multiple BBMs are expected to be implemented in routine clinical practice. However, BBM levels and performance can be affected by comorbidities such as cardiac disease and kidney function.[81,105] Moreover, the prevalence of amyloid pathology varies across races and ethnicities, which may influence predictive value.[106] Once these obstacles are addressed, BBMs can be adopted not only in dementia care setting but also in general health check-up examination in the future.

The introduction of anti-amyloid monoclonal antibodies, such as lecanemab and donanemab, into routine clinical practice highlights the increasing complexity of treatment decision-making in AD. Clinicians must now consider concomitant use with conventional symptomatic drugs, potential drug–drug interactions, and patient-specific contexts. While there is currently no clinical study evidence to support a contraindication, agents such as ginkgo biloba, selective serotonin reuptake inhibitors, and antipsychotics may raise theoretical concerns and require careful and sufficient monitoring. Beyond pharmacological considerations, ethical and clinical dilemmas remain regarding the use of lecanemab in asymptomatic individuals. Although the treatment paradigm may change based on the results of lecanemab and donanemab clinical trials in asymptomatic cognitively unimpaired individuals,[6,95,104] the use of anti-amyloid monoclonal antibodies in this population is currently not recommended. Special populations, including adults with Down syndrome, seizure disorders, or autoimmune diseases, may represent unique candidates, yet require further evidence to guide safe implementation. These nuanced scenarios emphasize that while lecanemab offers a landmark treatment option, its integration into diverse real-world clinical settings demands careful balancing of efficacy, safety, and patient-centered care. As maintenance regimens by monthly dosing and subcutaneous injection rather than intravenous infusion are recently introduced,[90] treatment options will be more available in future clinical settings.

In conclusion, the diagnosis of AD is now shifting from clinical symptom-oriented to biomarker-oriented, despite caution surrounding the use of biomarker alone. The emergence of anti-amyloid monoclonal antibodies as a disease-modifying treatment will facilitate the utilization of biomarker testing, especially BBMs, in the routine clinical settings.

Guideline for the special but common cases will be updated based on evidence-based observational studies, which clinicians should follow closely.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

Eosu Kim, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Hyun Woong Roh, Yoon Young Chang, Keun You Kim. Data curation: Keun You Kim. Formal analysis: Hyun Woong Roh, Yoon Young Chang. Funding acquisition: So Yeon Jeon, Sheng-Min Wang, Eosu Kim, Jae-Nam Bae, Seung-Ho Ryu. Methodology: Keun You Kim. Supervision: So Yeon Jeon, Sheng-Min Wang, Eosu Kim, Jae-Nam Bae, Seung-Ho Ryu. Writing—original draft: Hyun Woong Roh, Yoon Young Chang, Keun You Kim. Writing—review & editing: So Yeon Jeon, Sheng-Min Wang, Eosu Kim, Jae-Nam Bae, Seung-Ho Ryu.

ORCID iDs

Hyun Woong Roh	https://orcid.org/0000-0002-1333-358X
Yoon Young Chang	https://orcid.org/0009-0006-0279-1880
Keun You Kim	https://orcid.org/0000-0001-7192-2828
So Yeon Jeon	https://orcid.org/0000-0002-3656-1593
Sheng-Min Wang	https://orcid.org/0000-0003-2521-1413
Eosu Kim	https://orcid.org/0000-0001-9472-9465
Jae-Nam Bae	https://orcid.org/0000-0002-5024-6231
Seung-Ho Ryu	https://orcid.org/0000-0001-8057-8723

Funding Statement

This work was supported by a grant for task force activity from Korean Association for Geriatric Psychiatry (2024) and by Nano Material Technology Development Program through the National Research Foundation of Korea (NRF) funded by Ministry of Science and ICT (RS-2024-00450828).

Acknowledgments

The authors would like to express sincere thanks to all the board members of Korean Association for Geriatric Psychiatry, especially the members of Advisory Committee for the Guide to anti-amyloid monoclonal antibody therapy for Alzheimer's disease; Professors Sung Hwan Kim, Dong Young Lee, Kang Joon Lee, Jun-Young Lee, Chang Hyung Hong, Hong Jun Jeon, Sang Joon Son, Hong Jin Jeon, Il Han Choo, Hyun Kook Lim, and Dong Woo Lee.

REFERENCES

1. Chapleau M, Iaccarino L, Soleimani-Meigooni D, Rabinovici GD. The role of amyloid PET in imaging neurodegenerative disorders: a review. J Nucl Med 2022;63(Suppl 1):13S-19S.
2. Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016;15:673-684.
3. Mielke MM, Anderson M, Ashford JW, Jeromin A, Lin PJ, Rosen A, et al. Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease. Alzheimers Dement 2024;20:8216-8224.
4. Schindler SE, Galasko D, Pereira AC, Rabinovici GD, Salloway S, Suárez-Calvet M, et al. Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the global CEO initiative on Alzheimer's disease. Nat Rev Neurol 2024;20:426-439.
5. Palmqvist S, Whitson HE, Allen LA, Suarez-Calvet M, Galasko D, Karikari TK, et al. Alzheimer's Association clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. Alzheimers Dement 2025;21:e70535.
6. Rafii MS, Aisen PS. Amyloid-lowering immunotherapies for Alzheimer disease: current status and future directions. Nat Rev Neurol 2025;21:490-498.
7. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21.
8. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 2023;330:512-527.
9. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024;20:5143-5169.
10. Alzheimer A. [Übe eigenartige erkrankung der hirnrinde]. All Z Psychiatr 1907;64:146-148. German
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-III) (3rd ed). Washington, DC: American Psychiatric Association; 1980.
12. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-279.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR) (4th ed). Washington, DC: American Psychiatric Association; 2000.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5) (5th ed). Arlington: American Psychiatric Association; 2013.
15. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263-269.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944.
17. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280-292.
18. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119-128.
19. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118-1127.
20. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 2021;20:484-496.
21. Sperling RA; Alzheimer's Association Revised Criteria Workgroup. Alzheimer's disease begins years before symptoms: Alzheimer's Association Workgroup. Alzheimers Dement 2025;21:e107830.
22. Frisoni GB, Hansson O, Nichols E, Garibotto V, Schindler SE, Flier WM van der, et al. New landscape of the diagnosis of Alzheimer's disease. Lancet 2025;406:1389-1407.

23. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257-262.
24. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535-562.
25. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353-356.
26. Simuni T, Chahine LM, Poston K, Brumm M, Buracchio T, Campbell M, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol 2024;23:178-190.
27. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136-1139.
28. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 2014;10:844-852.
29. Jeon SY, Wang SM, Roh HW, Kim KY, Chang YY, Kim E, et al. Practical guide of the Korean Association for Geriatric Psychiatry to anti-amyloid monoclonal antibody therapy for Alzheimer's disease: focused on lecanemab. J Korean Med Sci 2025;40:e215.
30. Hansson O, Jack CR Jr. A clinical perspective on the revised criteria for diagnosis and staging of Alzheimer's disease. Nat Aging 2024;4:1029-1031.
31. Dubois B, Villain N, Schneider L, Fox N, Campbell N, Galasko D, et al. Alzheimer disease as a clinical-biological construct—an International Working Group recommendation. JAMA Neurol 2024;81:1304-1311.
32. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5-TR). Washington, DC: American Psychiatric Association Publishing; 2022.
33. Mattsson-Carlgren N, Andersson E, Janelidze S, Ossenkoppele R, Insel P, Strandberg O, et al. Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive tau PET in Alzheimer's disease. Sci Adv 2020;6:eaaz2387.
34. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med 2021;27:954-963.
35. Portelius E, Westman-Brinkmalm A, Zetterberg H, Blennow K. Determination of β-amyloid peptide signatures in cerebrospinal fluid using immunoprecipitation-mass spectrometry. J Proteome Res 2006;5:1010-1016.
36. Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease-preparing for a new era of disease-modifying therapies. Mol Psychiatry 2021;26:296-308.
37. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Mol Neurodegener 2021;16:10.
38. Vandermeeren M, Mercken M, Vanmechelen E, Six J, van de Voorde A, Martin JJ, et al. Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent assay. J Neurochem 1993;61:1828-1834.
39. Zetterberg H. Review: tau in biofluids—relation to pathology, imaging and clinical features. Neuropathol Appl Neurobiol 2017;43:194-199.
40. Skillbäck T, Rosén C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol 2014;71:476-483.
41. Ost M, Nylén K, Csajbok L, Ohrfelt AO, Tullberg M, Wikkelsö C, et al. Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. Neurology 2006;67:1600-1604.
42. Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, Vanmechelen E, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci Lett 2001;297:187-190.
43. Wang Y, Mandelkow E. Tau in physiology and pathology. Nat Rev Neurosci 2016;17:22-35.
44. Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol Chem Neuropathol 1995;26:231-245.
45. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjögren M, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neurosci Lett 2000;285:49-52.
46. Hampel H, Buerger K, Zinkowski R, Teipel SJ, Goernitz A, Andreasen N, et al. Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease: a comparative cerebrospinal fluid study. Arch Gen Psychiatry 2004;61:95-102.
47. Leuzy A, Janelidze S, Mattsson-Carlgren N, Palmqvist S, Jacobs D, Cicognola C, et al. Comparing the clinical utility and diagnostic performance of CSF P-Tau181, P-Tau217, and P-Tau231 assays. Neurology 2021;97:e1681-e1694.
48. Janelidze S, Stomrud E, Smith R, Palmqvist S, Mattsson N, Airey DC, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. Nat Commun 2020;11:1683.
49. Ashton NJ, Benedet AL, Pascoal TA, Karikari TK, Lantero-Rodriguez J, Brum WS, et al. Cerebrospinal fluid p-tau231 as an early indicator of emerging pathology in Alzheimer's disease. EBioMedicine 2022;76:103836.
50. Suárez-Calvet M, Karikari TK, Ashton NJ, Lantero Rodríguez J, Milà-Alomà M, Gispert JD, et al. Novel tau biomarkers phosphorylated at T181, T217 or T231 rise in the initial stages of the preclinical Alzheimer's continuum when only subtle changes in Aβ pathology are detected. EMBO Mol Med 2020;12:e12921.
51. Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. Lancet Neurol 2022;21:726-734.
52. Barthélemy NR, Li Y, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 2020;26:398-407.
53. Horie K, Barthélemy NR, Sato C, Bateman RJ. CSF tau microtubule binding region identifies tau tangle and clinical stages of Alzheimer's disease. Brain 2021;144:515-527.
54. Horie K, Salvadó G, Barthélemy NR, Janelidze S, Li Y, He Y, et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. Nat Med 2023;29:1954-1963.
55. Horie K, Barthélemy NR, Spina S, VandeVrede L, He Y, Paterson RW, et al. CSF tau microtubule-binding region identifies pathological changes in primary tauopathies. Nat Med 2022;28:2547-2554.
56. Salvadó G, Horie K, Barthélemy NR, Vogel JW, Pichet Binette A, Chen CD, et al. Disease staging of Alzheimer's disease using a CSF-based biomarker model. Nat Aging 2024;4:694-708.
57. Chang M. Roche diagnostics wins nod for Alzheimer's disease CSF test in Korea [Internet]. Available at: https://www.koreabiomed.com/news/articleView.html?idxno=21685. Accessed July 25, 2025.
58. Lee HS. Roche diagnostics' total-tau CSF test approved for Alzheimer's in Korea [Internet]. Available at: https://www.koreabiomed.com/news/articleView.html?idxno=25302. Accessed July 26, 2025.
59. Ovod V, Ramsey KN, Mawuenyega KG, Bollinger JG, Hicks T, Schneider T, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. Alzheimers Dement 2017;13:841-849.
60. Barthélemy NR, Salvadó G, Schindler SE, He Y, Janelidze S, Collij LE, et al. Highly accurate blood test for Alzheimer's disease is similar or

superior to clinical cerebrospinal fluid tests. Nat Med 2024;30:1085-1095.
61. Hampel H, Hu Y, Cummings J, Mattke S, Iwatsubo T, Nakamura A, et al. Blood-based biomarkers for Alzheimer's disease: current state and future use in a transformed global healthcare landscape. Neuron 2023;111:2781-2799.
62. Pais MV, Forlenza OV, Diniz BS. Plasma biomarkers of Alzheimer's disease: a review of available assays, recent developments, and implications for clinical practice. J Alzheimers Dis Rep 2023;7:355-380.
63. Milà-Alomà M, Tosun D, Schindler SE, Hausle I, Petersen KK, Li Y, et al. Timing of changes in Alzheimer's disease plasma biomarkers as assessed by amyloid and tau PET clocks. Ann Neurol 2025;98:508-523.
64. Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, et al. Head-to-head comparison of 8 plasma amyloid-β 42/40 assays in Alzheimer disease. JAMA Neurol 2021;78:1375-1382.
65. Montoliu-Gaya L, Benedet AL, Tissot C, Vrillon A, Ashton NJ, Brum WS, et al. Mass spectrometric simultaneous quantification of tau species in plasma shows differential associations with amyloid and tau pathologies. Nat Aging 2023;3:661-669.
66. Schindler SE, Petersen KK, Saef B, Tosun D, Shaw LM, Zetterberg H, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. Alzheimers Dement 2024;20:8074-8096.
67. Janelidze S, Bali D, Ashton NJ, Barthélemy NR, Vanbrabant J, Stoops E, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. Brain 2023;146:1592-1601.
68. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 2020;324:772-781.
69. Cogswell PM, Wiste HJ, Therneau TM, Griswold ME, Mattsson-Carlgren N, Palmqvist S, et al. Association of plasma Alzheimer's disease biomarkers with cognitive decline in cognitively unimpaired individuals. Alzheimers Dement 2025;21:e70625.
70. Palmqvist S, Warmenhoven N, Anastasi F, Pilotto A, Janelidze S, Tideman P, et al. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. Nat Med 2025;31:2036-2043.
71. Niimi Y, Janelidze S, Sato K, Tomita N, Tsukamoto T, Kato T, et al. Combining plasma Aβ and p-tau217 improves detection of brain amyloid in non-demented elderly. Alzheimers Res Ther 2024;16:115.
72. Kubota M, Bun S, Takahata K, Kurose S, Momota Y, Iwabuchi Y, et al. Plasma biomarkers for early detection of Alzheimer's disease: a cross-sectional study in a Japanese cohort. Alzheimers Res Ther 2025;17:131.
73. Wang J, Huang S, Lan G, Lai YJ, Wang QH, Chen Y, et al. Diagnostic accuracy of plasma p-tau217/Aβ42 for Alzheimer's disease in clinical and community cohorts. Alzheimers Dement 2025;21:e70038.
74. Shin D, Jang H, Yoo H, Kim K, Zetterberg H, Blennow K, et al. Potential utility of plasma pTau217 for assessing amyloid and tau biomarker profiles. Eur J Nucl Med Mol Imaging 2025;53:518-530.
75. Fernández Arias J, Brum WS, Salvadó G, Therriault J, Servaes S, Wang YT, et al. Plasma phosphorylated tau217 strongly associates with memory deficits in the Alzheimer's disease spectrum. Brain 2025;148:2384-2399.
76. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol 2020;19:422-433.
77. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol 2021;141:709-724.
78. Ashton NJ, Janelidze S, Mattsson-Carlgren N, Binette AP, Strandberg O, Brum WS, et al. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. Nat Med 2022;28:2555-2562.
79. Montoliu-Gaya L, Alosco ML, Yhang E, Tripodis Y, Sconzo D, Ally M, et al. Optimal blood tau species for the detection of Alzheimer's disease neuropathology: an immunoprecipitation mass spectrometry and autopsy study. Acta Neuropathol 2023;147:5.
80. Horie K, Salvadó G, Koppisetti RK, Janelidze S, Barthélemy NR, He Y, et al. Plasma MTBR-tau243 biomarker identifies tau tangle pathology in Alzheimer's disease. Nat Med 2025;31:2044-2053.
81. Kim KY, Kim E, Lee JY; Alzheimer's Disease Neuroimaging Initiative. Impact of amyloid and cardiometabolic risk factors on prognostic capacity of plasma neurofilament light chain for neurodegeneration. Alzheimers Res Ther 2024;16:202.
82. Teunissen CE, Verberk IMW, Thijssen EH, Vermunt L, Hansson O, Zetterberg H, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol 2022;21:66-77.
83. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry 2019;90:870-881.
84. Brum WS, Cullen NC, Janelidze S, Ashton NJ, Zimmer ER, Therriault J, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. Nat Aging 2023;3:1079-1090.
85. U.S. Food and Drug Administration. FDA clears first blood test used in diagnosing Alzheimer's disease [Internet]. Available at: https://www.fda.gov/news-events/press-announcements/fda-clears-first-blood-test-used-diagnosing-alzheimers-disease. Accessed September 9, 2025.
86. Kadakia KT, Dhruva SS, Ross JS, Burke JF, Johnston JL, Ramachandran R, et al. FDA authorization of therapeutic devices under the breakthrough devices program. JAMA Intern Med 2025;185:996-1004.
87. Klein G, Rabinovici GD, Zetterberg H, Tonietto M, Bittner T, Rukina D, et al. Interim biomarker results for trontinemab, a novel Brainshuttle™ antibody in development for the treatment of Alzheimer's disease. Alzheimers Dement 2025;21(Suppl 5):e104288.
88. McDade E, Cummings JL, Dhadda S, Swanson CJ, Reyderman L, Kanekiyo M, et al. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alzheimers Res Ther 2022;14:191.
89. The Medical Letter. In brief: once-monthly lecanemab (Leqembi) for Alzheimer's disease. Med Lett Drugs Ther 2025;67:64.
90. Eisai Co., Ltd. FDA approves LEQEMBI® IQLIK™ (lecanemab-irmb) subcutaneous injection for maintenance dosing for the treatment of early Alzheimer's disease [Internet]. Available at: https://media-us.eisai.com/2025-08-29-FDA-Approves-LEQEMBI-R-IQLIK-TM-lecanemab-irmb-Subcutaneous-Injection-for-Maintenance-Dosing-for-the-Treatment-of-Early-Alzheimers-Disease. Accessed August 30, 2025.
91. Eisai Co., Ltd. Eisai initiated rolling supplemental biologics license application to the U.S. FDA for LEQEMBI® IQLIK™ (lecanemab-irmb) as a subcutaneous starting dose for the treatment of early Alzheimer's disease under fast track status [Internet]. Available at: https://www.eisai.com/news/2025/news202560.html. Accessed August 30, 2025.
92. Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis 2023;10:362-377.
93. Wang H, Nery ESM, Ardayfio P, Khanna R, Svaldi DO, Shcherbinin S, et al. The effect of modified donanemab titration on amyloid-related imaging abnormalities with edema/effusions and amyloid reduction: 18-month results from TRAILBLAZER-ALZ 6. J Prev Alzheimers Dis 2025;12:100266.
94. Honig LS, Sabbagh MN, van Dyck CH, Sperling RA, Hersch S, Matta A, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. Alzheimers Res Ther 2024;16:105.
95. Rafii MS, Sperling RA, Donohue MC, Zhou J, Roberts C, Irizarry MC, et al. The AHEAD 3-45 study: design of a prevention trial for Al-

zheimer's disease. Alzheimers Dement 2023;19:1227-1233.
96. U.S. Food and Drug Administration. FDA to recommend additional, earlier MRI monitoring for patients with Alzheimer's disease taking Leqembi (lecanemab) [Internet]. Available at: https://www.fda.gov/media/188468/download. Accessed September 1, 2025.
97. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. Lancet Neurol 2021;20:930-942.
98. Wilcock DM, Schmitt FA, Head E. Cerebrovascular contributions to aging and Alzheimer's disease in Down syndrome. Biochim Biophys Acta 2016;1862:909-914.
99. Malle L, Patel RS, Martin-Fernandez M, Stewart OJ, Philippot Q, Buta S, et al. Autoimmunity in Down's syndrome via cytokines, CD4 T cells and CD11c+ B cells. Nature 2023;615:305-314.
100. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci 2018;20:63-73.
101. Reish NJ, Jamshidi P, Stamm B, Flanagan ME, Sugg E, Tang M, et al. Multiple cerebral hemorrhages in a patient receiving lecanemab and treated with t-PA for stroke. N Engl J Med 2023;388:478-479.
102. Ryan D, Zwischenberger BA, Liu AJ. Pearls and oy-sters: a patient on lecanemab newly diagnosed with atrial fibrillation. Neurology 2024;103:e210125.
103. Langa KM, Burke JF. Preclinical Alzheimer disease—early diagnosis or overdiagnosis? JAMA Intern Med 2019;179:1161-1162.
104. Pugh MAM. TRAILBLAZER-ALZ 3-a deeper dive into time-to-event trials. Alzheimers Dement 2023;19:e070865.
105. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, Vemuri P, Graff-Radford J, Machulda MM, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. Alzheimers Dement 2022;18:1128-1140.
106. Molina-Henry DP, Raman R, Liu A, Langford O, Johnson K, Shum LK, et al. Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial. Alzheimers Dement 2024;20:3827-3838.